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Tremor and Other Hyperkinetic Movements

Articles

Risk Factors for Tremor in a Population of Patients with Severe Mental Illness: An 18-year Prospective Study in a Geographically Representative Sample (The Curacao Extrapyramidal Syndromes Study XI)

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Abstract

Background: The aim was to assess incidence, prevalence and risk factors of medication-induced tremor in African-Caribbean patients with severe mental illness (SMI).

Method: A prospective study of SMI patients receiving care from the only mental health service of the previous Dutch Antilles. Eight clinical assessments, over 18 years, focused on movement disorders, medication use, and resting tremor (RT) and (postural) action tremor (AT). Risk factors were modeled with logistic regression for both current (having) tremor and for tremor at the next time point (developing). The latter used a time-lagged design to assess medication changes prior to a change in tremor state.

Results: Yearly tremor incidence rate was 2.9% and mean tremor point prevalence was 18.4%. Over a third of patients displayed tremor during the study. Of the patients, 5.2% had AT with 25% of cases persisting to the next time point, while 17.1% of patients had RT of which 65.3% persisted. When tremor data were examined in individual patients, they often had periods of tremor interspersed with periods of no tremor.

Having RT was associated with age (OR=1.07 per year; 95% confidence interval 1.03–1.11), sex (OR=0.17 for males; 0.05–0.78), cocaine use (OR=10.53; 2.22–49.94), dyskinesia (OR=0.90; 0.83–0.97), and bradykinesia (OR=1.16; 1.09–1.22). Developing RT was strongly associated with previous measurement RT (OR=9.86; 3.80–25.63), with previous RT severity (OR=1.22; 1.05–1.41), and higher anticholinergic load (OR= 1.24; 1.08–1.43).

Having AT was associated with tremor-inducing medication (OR= 4.54; 1.90–10.86), cocaine use (OR=14.04; 2.38–82.96), and bradykinesia (OR=1.07; 1.01–1.15). Developing AT was associated with, previous AT severity (OR=2.62 per unit; 1.64–4.18) and tremor reducing medication (OR=0.08; 0.01–0.55).

Conclusions: Long-stay SMI patients are prone to developing tremors, which show a relapsing–remitting course. Differentiation between RT and AT is important as risk factors differ and they require different prevention and treatment strategies.

Keywords: Tremor, Severe Mental Illness (SMI), Antipsychotic

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Ethics Statement: This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki. The authors' institutional ethics committee has approved this study and all patients have provided written informed consent.

Introduction

Tremors are rhythmic, involuntary, oscillatory movements of body parts.[1] In clinical psychiatric practice tremor is one of the most frequently occurring movement disorders[2] most often as a side effect of medication.[3] Tremor negatively influences quality of life, contributes to stigmatization,[2] and is an important reason for medication non-compliance.[2,3]

Tremors can be divided into resting tremor (RT) and action tremor (AT). AT can be further subdivided into postural, simple kinetic, and intention tremor.[4] In the literature, lithium, mood stabilizers, and antidepressants are described in relation to postural action tremors, which occur during voluntary muscle contraction or suspension against gravity[2,5] with a frequency of 4–12 Hz.[4] In contrast, antipsychotics appear to be associated more with parkinsonism with RT as part of its triad.[1,6] RT has a frequency of between 3 and 6 Hz and occurs when the affected limb, usually the hand, is fully supported against gravity.[4]

In general, patients with severe mental illness (SMI) are at high risk for developing movement disorders, given the fact that they are often exposed both to high doses and to polypharmacy.[7–9] Movement disorders include akathisia (4.5–9.3% prevalence[7,10,11]) tardive dyskinesia (28.4–39.7% prevalence[7,10]), dystonia (5.7–13.4% prevalence[10]), and parkinsonism (36.1–56.2%[7,10] prevalence). To our knowledge, no articles have been published focusing on tremor in SMI patients. Figures on tremor incidence and prevalence in SMI populations are difficult to find. While the literature suggests that about 40–50% of patients with medication-induced parkinsonism develop some form of tremor,[12] the incidence has never been studied. In addition, very little is known about risk factors for development and cessation of tremor in SMI populations.

The Curacao Extrapyramidal Syndromes study represents an 18-year follow-up of the SMI patients in a geographically circumscribed area.[10,13,14] The database represents a valuable opportunity to prospectively study tremor subtypes in a complete sample of SMI patients, in order to obtain population-based estimates of incidence, prevalence, and association.

Methods

Subjects

The protocol was approved by the Curaçao Institutional Review Board, and written informed consent was obtained by a psychiatrist from each patient. All patients were considered capable of making the decision to take part in the trial themselves, as the study had no risks for patients, required only a small time investment, and had possible benefits. Details on the Curacao Extrapyramidal Syndromes study, a longitudinal cohort study spanning eight measurements over 18 years, have been published in previous reports.[10,13,14] At baseline, data were gathered pertaining to all SMI patients (223) receiving care from the Capriles Hospital, the only psychiatric hospital in the Dutch Antilles and providing services to all patients with psychotic disorders on the islands. A baseline measurement was carried out in 1992 (N=162) followed by seven follow-up visits in 1993 (N=149), 1994 (N=129), 1996 (N=98), 1997 (N=94), 1998 (N=87), 2001 (N=114), and 2009 (N=87). Loss to follow-up was rare as patients rarely moved out of the catchment area and was mainly due to death. Inclusion criteria were 1) a history of antipsychotic medication use for at least 3 months; and 2) no obvious organic disorders that could cause movement disorders, such as Parkinson's disease. Essential tremor was not an exclusion criterion. Movement disorders were rated on 1) the Unified Parkinson's Disease Rating Scale (UPDRS)[15] for tremor, bradykinesia, and rigidity; 2) the Abnormal Involuntary Movement Scale (AIMS)[16] for tardive dyskinesia; and 3) the Barnes Akathisia Rating Scale (BARS)[17] for akathisia. Rating was achieved by consensus and the inter-rater reliability kappa for tremor was 0.70; a detailed description of the test situation can be found in previous publications.[10] The UPDRS version 3.0 only includes the postural subtype of AT; hence, all AT in this article are postural. All movement disorders were assessed in person by the same two raters (P.v.H and G.M.), both psychiatrists specialized in movement disorders in psychiatry; medication data and diagnosis were extracted from patient records by trained clinicians and all patients gave informed consent. Patients with mental retardation (N=3) and dementia (N=7) were excluded as they were not considered SMI disorders. Patients who had undergone a lobotomy (N=22) were also excluded. This resulted in a dataset of 191 SMI patients; 162 patients were included at T0 and a further 29 (SMI day treatment patients) were included at T1.

Demographic variables such as age, sex, DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised) diagnosis, and cocaine use were collected from records at time of inclusion. Medication data were collected at all time points and were converted to defined daily doses (DDDs).[18] Information on the type of antipsychotic, i.e., first-generation antipsychotic or second-generation antipsychotic, and the route of administration, oral or depot, was collected. The total anticholinergic load of the combined medication was calculated for each patient by summing the anticholinergic load pertaining to each medication according to the Anticholinergic Drug Scale (ADS).[19] The ADS assigns a score to each medication (ranging from 0 to 3) in accordance with the level of anticholinergic action of the compound.

Tremor-protective medication was defined as beta-blockers (propranolol and sotalol) and dopamine agonists (levodopa and carbidopa). Lithium, antidepressants and other medication were considered tremor inducing if they were listed by Arbaizar et al.,[2] Morgan and Sethi,[3] Puschmann and Wszolek,[5] and Zeng et al.[20] or had at least 1% risk of tremor according to the Dutch pharmaceutical reference manual.[21] Antipsychotics were not included in this category as they were already represented separately in the total antipsychotic DDD.

RT was dichotomously defined as a severity score of at least mild (a score of 2, range 0–4) on the RT subscale (item 3) and AT as a severity score of at least mild on the AT subscale (item 4) of the UPDRS.[15] Movement disorder variables were continuous and defined as 1) the sum of items 1–7 of the AIMS for tardive dyskinesia; 2) item 4 of the BARS for akathisia; 3) the sum of the sub items of item 5 of the UPDRS for rigidity; and 4) the sum of items 1, 2, 6–12, and 14 of the UPDRS for bradykinesia.

Descriptive statistics

At each time point prevalence was calculated. In addition, the 18-year average prevalence was calculated over all time points. Incidence rates were calculated by dividing the number of new cases by the number of person-years of follow-up.

Regression models

All analyses were performed using STATA.[22] As all assessments of each subject were included in the analyses, data had a multilevel structure with multiple assessments clustered within subjects. The Stata xtlogit command is ideally suited to analyze this type of data. The obtained odds ratios can be interpreted as odds ratio results obtained from unilevel logistic regression. The dependent variable was the dichotomized tremor variable. Effect sizes of the risk factors were expressed as odds ratios and their 95% confidence interval (CI). To assess which factors were related to the development or cessation of a tremor type over time, a time-lagged analysis was performed, using the xtlogit random effects procedure. In this analysis, the dichotomous tremor type was the outcome, while the same dichotomous tremor type and clinician-influenced variables at the previous time point were entered as independent variables.

Results

Demographic characteristics

Of the 191 patients included, 162 were included at baseline and 29 were included at the first follow-up measurement, resulting in a total of 876 observations. Most (95.4%) were of African-Caribbean origin. At baseline, mean age was 50 (SD 16) years; men were 47 (SD 14) and women 58 (SD 19) years. The primary diagnoses according to DSM-III-R were schizophrenia (80.2%), affective disorder (5.1%), and other (14.7%). Information about medication use at baseline is displayed in Table 1.

Tremor prevalence and incidence

Over a third of patients had tremor at least once during the study. Overall, the average prevalence of the combined RT and AT outcome (hereafter combined tremor) was 18%, with a time-specific distribution of 15%, 23%, 25%, 18%, 16%, 13%, 21%, and 15% over the consecutive time points. RT occurred at an average prevalence of 17%, with a time-specific distribution of 14%, 21%, 22%, 18%, 15%, 13%, 20%, and 14% over the consecutive time points. AT had a lower rate at an average prevalence of 5% and a time-specific distribution of 4%, 3%, 7%, 2%, 6%, 2%, 11%, and 7% over the consecutive time points.

Longitudinally, tremors displayed a relapsing–remitting course; in two-thirds of cases the combined tremor at one time point was also present at the next time point. AT persisted less frequently than RT (25% and 67% persistence to next time point, respectively). Incidence rates were 29 per 1000 person-years (2.9%) for all tremors; 26 per 1,000 person-years, or 2.6% (95% CI 1.9–3.6%), for RT and 12 per 1000 person-years, or 1.2% (95% CI 0.8–1.9%), for AT. The number of patients displaying a first time tremor is balanced by the number of patients permanently remitting for tremor resulting in a flat tremor prevalence over time despite the incidence of new tremor cases.

Risk factor analysis

The results of the risk factor analyses are described in Table 2. Three separate analyses were done: one on combined tremor, one on RT and AT types.

The combined tremor analysis

The multilevel logistic regression yielded significant odds ratios (OR) between combined tremor and age (OR 1.06 per year), sex (reference male; OR 0.18) and cocaine use (OR 8.32) Of the other movement disorders, bradykinesia (OR 1.14 per unit UPDRS increase), but not rigidity (OR=1.09), was positively associated with tremor while dyskinesia (OR 0.92 per unit AIMS increase) displayed a negative association. Of the medication variables, only the number of tremor-inducing medications (OR 2.23 per added medication) was significantly associated with tremor.

Tremor subtype analysis

Cocaine use (OR 10.53 for RT and 14.04 for AT) and bradykinesia (OR 1.16 for RT and 1.07 for AT) were associated with both tremor types. Age (OR 1.07), sex (OR 0.19), and dyskinesia (OR 0.90) were associated only with RT. Although for age and sex the odds ratio is similar in both tremor types, the number of AT cases, however, is smaller than the number of RT cases (48 AT cases versus 161 RT cases). The number of tremor-inducing medications other than antipsychotics (OR 4.54) was significantly associated only with AT.

Time-lagged regression analysis

The results of the time-lagged analyses are described in Table 3. For the combined tremor analysis, previous combined tremor (OR 7.87) and previous tremor severity (OR 1.20 per point on the UPDRS) were significantly associated with current tremor. Of the medication variables, previous higher anticholinergic load was associated with more tremor (OR 1.19), whereas previous depot medication (OR 0.29) was associated with less tremor.

In the tremor RT and AT subtype analysis only previous tremor severity was significantly associated with both subtypes. RT was strongly associated with previous RT (OR 9.86), but previous AT was not significantly associated with previous AT (OR 0.24). Medication variables also had different effects on resting and action tremors compared with the combined tremor. Previous number of tremor-reducing medications (OR 0.08 per medication) was negatively associated with AT at the next time point. Previous depot medication did not predict either type of tremor subtype; however, the effect size for RT (0.33) was similar to the effect size for the combined tremor outcome (0.29).

Discussion

To our knowledge this is the first long-term follow-up study on medication-induced tremor in SMI patients, which demonstrates that tremor is a frequently occurring relapsing–remitting disorder with over

Table 1. **Demographic Characteristics, Movement Disorder Prevalence, and Medication Use at Baseline**

	No Tremor		Resting Tremor[1]		Action Tremor[1]		All Patients	
	N	%*	N	%*	N	%*	N	%*
Demographic variables								
Subjects	137	85	22	14	6	4%	162	100%
Age, mean SD	50.12	16.77	50.17	13.48	58.28	19.45	50.43	16.45
Male sex	94	69%	20	91%	5	83%	116	72%
Cocaine use	23	17%	5	23%	1	17%	28	17%
Diagnosis schizophrenia	112	82%	17	77%	3	50%	130	80%
Movement disorders								
Dyskinesia	19	14%	3	14%	1	17%	22	14%
AIMS mean SD	6	4.11	6	4.58	2		6	4.06
Akathisia	5	11%	1	5%	0	0%	16	10%
BARS mean SD	2.53	0.74	4				2.63	0.81
Bradykinesia	32	23%	9	41%	4	67%	42	26%
UPDRS[2] mean SD	14.81	6.71	15.22	8.89	19	7.53%	14.93	7.03
Rigidity	22	16%	7	32%	2	33%	29	18%
UPDRS[3] mean SD	8.64	3	6.71	3.77	9.5	3.54%	8.17	3.24
Medication variables								
Antipsychotic type								
No AP	16	12%	0	0%	1	17%	17	10%
FGA only	115	84%	20	91%	4	67%	137	85%
SGA only	5	4%	2	9%	1	17%	7	4%
Both AP types	1	1%	0	0%	0	0%	1	1%
AP DDD mean SD	1.58	1.48	2.05	1.88	1.12	0.78	1.62	1.53
Depot use	81	59%	15	68%	3	50%	97	60%
Tremor-inducing medication use	37	27%	4	18%	2	33%	43	27%
Tremor-reducing medication use	3	2%	0	0%	0	0%	3	2%
Anticholinergic load	2.58	2.55	3.41	2.54	3.5	1.97	2.72	2.55
Benzodiazepine DDD	0.23	0.64	0.34	0.7	0.08	0.2	0.24	0.64

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; AP, Antipsychotic; BARS, Barnes Akathisia Rating Scale; DDD, Defined Daily Dose; FGA, First-generation Antipsychotic; SGA, Second-generation Antipsychotic; UPDRS, Unified Parkinson's Disease Rating Scale.
[1]Patients can have both action and resting tremor.
[2]List items bradykinesia.
[3]List items rigidity.
*Numbers in percentages except when stated otherwise.

Table 2. **Relationship between Covariates and Tremor Subtypes in Psychiatric Patients with Severe Mental Illness, 18-year Follow-up Data**

	Any Tremor			Resting Tremor			Action Tremor		
	OR	95% CI		OR	95% CI		OR	95% CI	
Demographic variables									
Age	1.06**	1.02	1.10	1.07**	1.03	1.11	1.05	1.00	1.11
Sex	0.18*	0.05	0.69	0.19*	0.05	0.78	0.18	0.032	1.07
Cocaine use	8.32**	2.01	34.4	10.53**	2.22	49.94	14.04**	2.38	82.96
Diagnosis	2.42	0.66	8.87	2.17	0.53	8.90	2.26	0.49	10.35
Other movement disorders									
Dyskinesia	0.92*	0.86	0.99	0.90**	0.83	0.97	1.04	0.95	1.15
Akathisia	1.32	0.88	1.98	1.30	0.84	2.01	1.34	0.74	2.44
Bradykinesia	1.14***	1.08	1.21	1.16***	1.09	1.22	1.07*	1.01	1.15
Rigidity	1.09	0.99	1.21	1.09	0.98	1.22	1.10	0.96	1.27
Medication variables									
Benzodiazepine DDD	1.18	0.77	1.81	1.14	0.70	1.84	1.37	0.78	2.38
No antipsychotic use (base = only FGA)	0.57	0.13	2.51	0.54	0.11	2.57	1.75	0.27	11.51
Only SGA use (base = only FGA)	0.42	0.11	1.56	0.51	0.13	2.01	1.00	0.17	5.76
Both FGA and SGA (base = only FGA)	0.48	0.11	2.08	0.47	0.10	2.42	0.69	0.09	5.23
Antipsychotic DDD	1.12	0.84	1.48	1.13	0.84	1.53	0.97	0.66	1.45
Depot use (base= no)	2.15	0.90	5.17	2.14	0.85	5.40	1.65	0.47	5.81
Number of tremor inducing medications	2.23*	1.10	4.52	1.83	0.86	3.92	4.54***	1.90	10.86
Number of tremor reducing medications	0.71	0.09	5.76	0.45	0.05	4.21	5.94	0.63	55.94
Anticholinergic load	0.99	0.85	1.16	0.97	0.82	1.15	1.15	0.93	1.42

Abbreviations: CI, 95% Confidence Interval; DDD, Defined Daily Dose; OR, Odds Ratio; FGA, First-generation Antipsychotic; SGA, Second-generation Antipsychotic.
*p<0.05; **p<0.01; ***p<0.001.

a third of patients having tremor at least once during the 18 years of the follow-up. In two-thirds of the SMI patients tremors were present at the next assessment with the more severe tremor forms being more likely to be present at the next time point. The importance of the distinction in RT and AT should be noted, as each tremor type is associated with different medication and demographic variables. Tremor is highly noticeable and is often associated with shame, stigma, and physical handicap; active assessment, treatment and prevention of tremor is therefore of great clinical importance.[2,3]

Since most previous studies used a cross-sectional model and did not focus on the vulnerable subgroup of SMI patients, it is difficult to compare prevalence rates. Bakker et al.[7] found an average of 20% for combined tremor prevalence and a prevalence of 14% and 16% for RT and AT respectively. The higher AT prevalence could be

Table 3. **Time-lagged Relationship between Covariates and Tremor Subtypes in Psychiatric Patients with Severe Mental Illness, 18-year Follow-up Data**

	All Tremor			Rest Tremor			Action Tremor		
	OR	95% CI		OR	95% CI		OR	95% CI	
Having tremor at the previous time point	7.87***	3.45	17.94	9.86***	3.80	25.63	0.24	0.03	1.96
Severity of tremor	1.20***	1.08	1.34	1.22**	1.05	1.41	2.62***	1.64	4.18
Medication variables									
Change in benzodiazepine dose	0.90	0.68	1.28	0.72	0.48	1.08	1.59	0.91	2.79
Change in antipsychotic dose	0.88	0.67	1.14	0.91	0.69	1.20	0.98	0.68	1.43
Switching antipsychotics	0.84	0.38	1.89	0.70	0.29	1.68	0.79	0.21	2.98
Getting depot medication	0.29*	0.09	0.94	0.33	0.10	1.09	0.89	0.14	5.52
Stopping depot medication	1.97	0.60	6.50	2.04	0.60	6.94	1.90	0.29	12.32
Number of tremor inducing medications	0.56	0.30	1.06	0.67	0.34	1.34	0.45	0.17	1.18
Number of tremor reducing medications	0.27	0.04	1.71	0.63	0.11	3.72	0.08*	0.01	0.55
Anticholinergic load	1.19*	1.04	1.37	1.24**	1.08	1.43	1.10	0.88	1.38

Abbreviations: CI, 95% Confidence Interval; DDD, Defined Daily Dose; OR, Odds Ratio; FGA, First-generation Antipsychotic; SGA, Second-generation Antipsychotic.
*p<0.05; **p<0.01; ***p<0.001.

attributed to a different composition of the population. In the study by Bakker et al. 13.5% of patients had an affective disorder as primary diagnosis, in contrast to only 5.1% of patients in the current study. While Bakker et al. did not collect data on antidepressant and lithium use, both medications known to induce AT, it is to be expected that they would be prescribed more frequently than in the current study.

The relapsing–remitting course of both tremor subtypes indicates that environmental factors, such as medication or cocaine use, play an important role in the development and cessation of tremor. The relationship between age and RT is in line with previous research.[3] The association between cocaine use and both tremor types has been described before,[2,3] whereas the association between sex and parkinsonism is found inconsistently.[12]

The risk factor analysis in the current study further underlines the difference between RT and AT by their difference in association with other movement disorders. As RT is part of the parkinsonism triad (RT, bradykinesia, and rigidity),[6] it is associated with bradykinesia as expected. However, RT was not associated with rigidity, even though the relationship between drug-induced parkinsonism and rigidity has been extensively described.[12,23] This could be in line with the subdivision of Parkinson's disease in tremor-dominant and rigidity-gait disturbance subtypes, which have different underlying neuropathological mechanisms.[24]

There was also a significant association between AT and bradykinesia. Medication-induced parkinsonism can sometimes present with postural action rather than RT[12] and with more severe tremors it is sometimes difficult to differentiate between the tremor types.[4] Dyskinesia on the other hand was solely and inversely associated with RT as described in other studies[25] and is sometimes suggested that parkinsonism and dyskinesia are at the other ends of the spectrum of basal ganglia disorders.[6]

AT was associated with medication, other than antipsychotics, known to induce tremor, as has been extensively described in the literature.[2,3] However, no relationship was found between RT and antipsychotic type or dose, even though antipsychotic medication is considered a primary cause for drug-induced parkinsonism.[12,23] The most likely explanation is that the effect of antipsychotic dose on tremor is obscured due to the high doses of antipsychotics most patients receive.

The time-lagged analysis was added to ascertain if there was the temporal relationship between adapting medication and a subsequent change in tremor status. This temporal relationship is one of the Bradford Hill guidelines[26] and is an argument for causality. The fact that there seems to be a strong relationship (OR 0.08) between adding a beta-blocker and the cessation of AT makes it highly likely that

there is a causal relationship. The time-lagged models also showed a strong association between previous tremor severity and previous tremor. There was also a relationship between any type of tremor and receiving depot medication. Because this relationship could not be replicated in the tremor subtypes it is possible that this relationship is spurious. It is also possible that the small number of depot changes has left this variable underpowered.

Surprisingly, a higher anticholinergic load led to a higher risk of tremor in the following assessment, for which different explanations could be given. Firstly, clinicians might treat the parkinsonism spectrum of bradykinesia and RT[12] with an anticholinergic high enough to reduce bradykinesia but not to reduce RT, owing to anticholinergic side effects, such as a dry mouth, constipation, cognitive problems. Secondly, anticholinergics may not be entirely effective in treating RT in SMI patients. Mena and Yébenes,[23] Caroff et al.[27], and Dayalu and Chou[28] noted the paucity of evidence supporting anticholinergic treatment of drug-induced parkinsonism. Mena and Yébenes even stated that there is little rational for it.

Strengths

The inclusion of all inpatients (and outpatient clinic treatment patients) of a restricted area reduces selection bias. Second, the long follow-up period of 18 years with eight assessments over time increases the validity of the findings. Third, loss to follow-up, which mainly was by death, was limited, further reducing selection bias. Last, all measurements were done by the same two raters, both psychiatrists specializing in movement disorders (P.v.H. and G.M.), increasing the reliability.

Limitations

The study population was already ill and taking antipsychotics for, on average, 20 years before inclusion. For an incidence study it would be more appropriate to include a population with no history of psychopharmacology. Prevalence and risk factors for persistence, as described in this article, may be more suitable to describe a relapsing–remitting disorder such as tremor in a SMI population. Secondly, the UPDRS does not really provide an in-depth examination of tremor, as it focuses on parkinsonism symptoms as a whole. For this study a rating scale focusing solely on tremor would have been better suited. However, the UPDRS is a valid and reliable rating scale that measures each of the three core symptoms of parkinsonism: bradykinesia, rigidity, and tremor. Thirdly, it may be argued that a slight (score 1, range 0–5) rest tremor is already abnormal and the cut off for RT should therefore be lowered from mild (score 2) to slight. We examined the results of lowering the cut off in a post hoc analysis and found that this resulted in more extreme odds ratios and lower p-values for the variables in the risk analysis. In the time-lagged analysis the same occurred for previous tremor status and previous tremor severity. However, the relationship between anticholinergic load and rest tremor now has a p-value of 0.51 making it non-significant. Also essential tremor was not an exclusion criterion for the study as in the time-lagged analysis design; patients are their own controls and a pre-existing tremor should not influence results. When the analyses are redone excluding the four patients who had a pre-existing AT results are nearly identical. Finally it would have been preferable to ascertain cocaine use not only via medical records but also via urine toxicology and to also register patient alcohol use.

In conclusion, medication-induced tremor is a frequently occurring relapsing-remitting disorder with serious adverse effects for patients. For clinicians it is important to differentiate between postural action and RTs as both are caused by different types of medication and require different treatment.

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